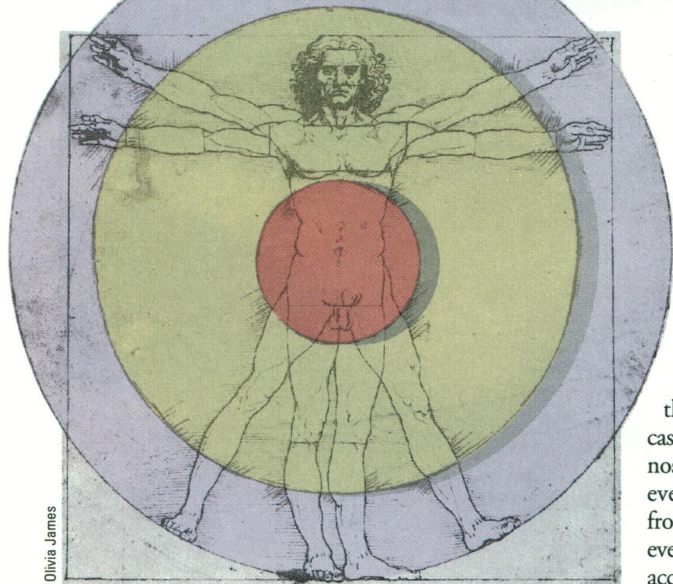


Assault on the Male



According to Tom Bruckman, men and women are not created equal—when it comes to researching the sex-specific cancers that strike and kill them. In 1994, the National Cancer Institute spent five times more (\$267 million) studying breast cancer than prostate cancer (\$57 million), points out Bruckman, the executive director of the American Foundation for Urologic Disease. But the fact that prostate cancer is now the number one cancer detected in men, and the number two cause of cancer deaths among men, has begun to mobilize its victims. “Support groups have exploded into action,” says Bruckman. “Four years ago, there were about 10 groups across the country. Now there are almost 500. We are learning from the experience women have had in lobbying for research and in helping themselves out.”

The facts are indeed scary. Not only is the rate of prostate cancer growing in elderly men (it accounts for 92% of male cancers), but its brother, testicular cancer, is also increasing (its incidence has doubled in the last 50 years), and is now the most common malignant disease in young men. And then there is the ongoing, ominous debate about falling sperm levels.

But the sex-selective cancers do share some depressing similarities. This year, more than 244,000 men will be diagnosed with prostate cancer, and about 40,000 will succumb. About 183,000 women will develop breast cancer, and 46,240 will die. Other sex-selective cancers such as cancer of the cervix, ovary, and uterus, will account for 26,400 deaths, while testicular and other

male reproductive cancers will kill 580 men annually.

Breast cancer can affect one in eight women, if they live long enough, and 13% of men develop clinically significant prostate cancer at some time in their lives, usually late in life. The NCI says that every 3 minutes, a new case of prostate cancer is diagnosed in the United States, and every 15 minutes a man dies from it. One-third of them will eventually die from the disease, according to the NCI.

The statistics are bad enough, says Bruckman, but what really scares men is the knowledge that after age 45, the prostate starts changing. No one can predict if that transformation will result in a painful, but cancer-free, enlargement or a slow-growing carcinoma that, when it finally produces symptoms, is often too advanced to cure. Metastasized prostate cancer is fatal because chemotherapy can't target the slow-growing carcinoma. Prostate cancer increases faster with age than any other major cancer; researchers have found that by age 80, approximately 60–70% of men have evidence of incidental carcinoma at autopsy. By the year 2000, the incidence of prostate cancer is expected to increase by 90%, and deaths will rise by 37%.

What prostate cancer shares with breast cancer, according to Stanford epidemiologist Alice Whittemore, a leading prostate cancer researcher, is that “there are no neat models to tie all the risk factors together: those things you eat, are exposed to, and how your genetic disposition handles everything. We know so little about what causes these diseases.”

This is also true of testicular cancer. Although cancer of the testis is a disease of young men and is highly treatable, researchers don't know what causes it, or even if it is related in some fashion to other male genital cancers. The glands share hormonal influences. Testosterone, the male hormone, is made in the testicles

and is the substance that makes the 1.5-inch walnut-shaped prostate develop and stimulates it to manufacture secretions for sperm. The question for researchers is which men are at risk for cancer of their reproductive system and why.

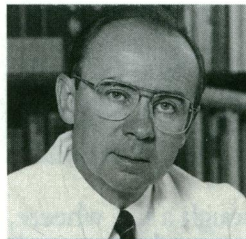
A Fat Risk?

Like any good mystery, there are many clues leading researchers down disparate avenues, often to contradictory evidence. “I don't know if any one theory holds the truth or is flawed,” said Johns Hopkins Urologist-in-Chief Patrick Walsh. “All we can say is that there are a number of intriguing leads, so nothing should be dismissed.”

The first clue to teasing apart influences on prostate cancers is population studies that revealed up to one-third of all men examined at autopsy are found to have microscopic, incidental prostate cancer. And this 30% incidence is found in men around the world, so it is likely caused by some universal factor such as age. In some men, this latent cancer never becomes a problem, but in others it kills them. Death rates vary dramatically from country to country. A 1982 study by the International Agency for Research on Cancer, in Lyon, France, looked at prostate cancer incidence in five continents and found a 25-fold difference between incidence rates in black American men living in San Francisco and Japanese men. In 1990, a team from Johns Hopkins, led by urologist John Isaacs, further refined the comparison, concluding that the initiation rate of prostate cancer was the same in Japanese and American men, but that there appeared to be differences in the rate of promotion or progression to clinically evident prostate cancer. Their observations were supported by other studies that found that immigrants who

move from low-risk areas to the United States assume Americans' higher risks.

So what are the risk factors that increase the chance of the cancer progressing in American men, but cause very few Japanese men to die of prostate cancer? One obvious environmental culprit is the fatty Western diet, which is said to contribute to a number of cancers, including breast and colon,



Patrick Walsh—Genetic linkages may soon provide insights into prostate cancer.

colon, but not testicular. As early as 1975, researchers found that prostate cancer death in 32 countries was highly associated with total fat consumption, a finding similar to that for breast cancer. Follow-up studies have also made the case for diet. A 1993 Harvard study of 48,000 men found that those men who consumed high amounts of saturated and unsaturated fats had the highest risk of ending up with advanced or fatal cases of prostate cancer, but there was no association between fat intake and early stages of prostate cancer. Taking these findings a step further, the research team, led by Edward Giovannucci and Walter Willett, discovered a link between the disease and a type of fat called alpha-linolenic acid, which is found in meat as well as in dairy products and other foods.

This May, results of a four-year case-control study of prostate cancer among men of different ethnic and racial backgrounds living in five locations confirmed that fat is a risk factor for advanced cancer, but this time it was saturated fat. The study led Stanford's Whittemore to conclude that there is a "causal role in prostate cancer for saturated fat intake, but the data suggest that other factors are largely responsible for interethnic differences in risk. Fat is definitely a factor, but there are others," she says.

Researchers are also studying ways that fat could promote cancer. Some say it may dramatically affect prostate cell membranes, altering them in such a way that cells are more likely to turn cancerous. Another theory is that a diet high in animal fat raises a man's level of testosterone, which in turn bolsters the likelihood that cancerous cells will multiply and form a tumor.

The answer is not simple. For example, a high-fat diet is believed to play a role in other diseases, such as colon and breast cancer. The death and incidence rates of prostate cancer are higher among American blacks than American whites, yet the incidence of breast and colon cancer is about the same in the two groups. If fat is the culprit, why isn't the rate of prostate cancer as high in whites?

Other researchers point to different aspects of the diet that could influence cancer. An experiment reported in the March 1 issue of the *Journal of the National Cancer Institute* found modified citrus pectin, given orally to rats, inhibited spontaneous metastasis in prostate cancer. The researchers, from the Michigan Cancer Foundation and University of Michigan School of Medicine, found that modified citrus pectin, a complex polysaccharide, inhibited the adhesion of

prostate cancer cells to rat endothelial cells. In other labs, scientists have linked deficiencies in vitamin A, a fat-soluble vitamin found in yellow vegetables, to development of different kinds of tumors. But the type of vitamin A seems to matter: supplements of one kind of vitamin A, beta-carotene, found in certain vegetables, appear to lower risk of prostate cancer, while other forms of vitamin A, found in animal fat, raise it.

Another vitamin seems to be related to geographic incidence of prostate cancer. A 1992 study in the journal *Cancer* demonstrated a global north-south graduated pattern of prostate cancer, with the highest rates in the north. The theory explored by the authors, Carol Hanchette and Gary Schwartz of the University of North Carolina at Chapel Hill, is that insufficient levels of vitamin D from UV radiation may increase the chance of the

cancer. It could explain a number of observations, say the authors, such as why more men in the Scandinavian countries, Canada, and the United States have prostate cancer than men in Asia, and why black men are susceptible—people with dark skin absorb less sunlight and thus have lower levels of vitamin D.

Genetic Mechanisms

There are some clues about the inheritability of prostate cancer. A 1992 study by Johns Hopkins researchers Bob Carter and Patrick Walsh, published in the 15 April 1992 issue of the *Proceedings of the National Academy of Science*, showed for the first time the close association between a family history of prostate cancer and a man's likelihood of developing the disease early in life. Says Walsh, "Your risk of the disease is twice as high if your father or brother has it. But the risk could grow to 90 percent depending on the number of affected relatives you have and the age at which they develop the disease." But researchers say this familial form of prostate cancer probably accounts for only about 10% of the cases, similar to the inheritability of breast cancer. And they suspect it is autosomal dominant—a single gene from the mother or father can lead to development of disease. But the "prostate gene" has not been mapped yet. "I think genetic linkages are bound to give us paydirt soon, but there are a number of interesting leads on environmental factors, as well," says Walsh. "Nothing should be dismissed."

Late last year, researchers in another Johns Hopkins laboratory identified a genetic alteration linked to prostate cancer that



Alice Whittemore—There are no models to tie all the risk factors together.

Stanford U.

Facts



Every three minutes a man is diagnosed with prostate cancer in the United States. Every 15 minutes a man dies from it.



Prostate cancer is the number one cancer detected in men and the number two cause of cancer deaths among men. Testicular cancer is the most common malignant disease in young men.



This year, 244,000 men will be diagnosed with prostate cancer and 40,000 will die from it. Comparatively, 183,000 women will be diagnosed with breast cancer and 46,240 will die.

they believe is the most frequently occurring genetic error associated with the disease. In almost all of the human prostate cancer samples he studied, oncologist and urologist William Nelson found deactivation of the gene that codes for glutathione S-transferase (*GSTP1*), an enzyme that detoxifies environmental carcinogens. He also found that some men with noncancerous prostate tumors produce the enzyme while others don't, indicating that alteration of the gene may cause the tumors to become cancerous. Nelson noted that diet and genes may form an "alluring" nexus in this situation: "Vegetables like broccoli and brussels sprouts trigger high production of these enzymes." Inherited gene mutations likely speed up initiation of the cancer, and environmental

events may promote it or protect against it, Nelson says.

In May, a major gene discovery offered the hope of a test to predict the course of prostate cancer in individuals and hope of corrective gene therapy. Johns Hopkins researcher John Isaacs and Carl Barrett, head of the NIEHS's molecular carcinogenesis laboratory, identified a gene, called *KAI1*, that prevents prostate cancer cells from metastasizing, or spreading out from the gland. It is only the second human gene known to block deadly metastasis. The gene's action had been shown in mice injected with human prostate cancer. According to Barrett, the research team first proved that metastatic prostate cancer cells lacked the *KAI1* gene, but that it was present in prostate cancers that didn't spread. The gene was isolated, injected into cultures of human prostate cancer cells, and then transferred to mice. These mice had much less cancer spread than mice without the gene. "We don't know how this gene affects the invasive ability of cells, but it is quite unique. Most genes found to date in cancer regulate the growth of cells," says Barrett. "We want to identify what factor, potentially environmental, that causes the gene to turn off." Currently, Barrett is trying to determine whether *KAI1*'s effects are limited to prostate cancer, and the Johns Hopkins team is looking to see if the *KAI1* gene was absent in cancer that spread in 200 prostate cancer patients.

There have been few leads on the genetic influences of testicular cancer, which is expected to be diagnosed in 7,100 American men this year, killing 370. No clear abnormalities in known oncogenes or tumor-suppressor genes have been linked to testicular cancer, according to University of Chicago urologist Robert Smith. Smith reported in May in the *Journal of Urology* that evidence from his laboratory points to the possibility that one or more tumor-suppressor genes are inactivated on chromosome 11, near where a tumor-suppressor gene for Wilms' tumor, a cancer of the kidney that particularly affects children, and for gonadoblastomas have been found. Smith said it appears that these genes may be important, although "it is likely that testicular cancer results from a multistep process involving alterations in many genes."

Many scientists point to abnormalities in the development of the testes as a risk factor. Research at Oxford University found 32% of patients with the cancer had atrophy of the testis, and 75% may have reduced sperm count. These results point to another pre-



Gail Prins—There is a compelling case for the effects of estrogen on the prostate.

Michael Reese Hospital

dominant risk category for both testicular and prostate cancer: natural and synthetic estrogens.

Hormonal Balance

The first hint that the level of sex hormones circulating in men had an impact on male reproductive cancer was the observation that prostate cancer is rarely found in men with undeveloped testes and in castrated men. The evidence has since been stacking up to form an alarming picture that paints estrogen and testosterone as cancer culprits.

The prostate and the testes are regulated by sex hormones called androgens, which are made in the testes. Foremost among these hormones is testosterone, produced in the testes but controlled by a hormone from the pituitary gland, called luteinizing hormone (LH). Testosterone circulates in the blood and enters the prostate gland by diffusion, where it is transformed by an enzyme into the hormone dihydrotestosterone (DHT), which is more than twice as potent as testosterone. Both hormones can bind to the same receptors on the prostate cell, which activates genes. During this process, the hypothalamus monitors the amount of testosterone in the blood and boosts or cuts back on production of LH. Estrogens can promote or retard the process naturally, but the precise mechanisms of how a hormonal imbalance leads to cancer is not yet understood. Environmental estrogens mimic the action of natural estrogens; they have the same chemical key that can turn hormone production on or off.

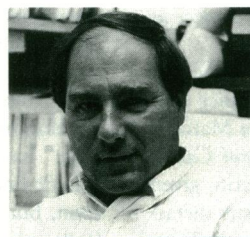
Conversely, estrogen receptors can be blocked by weak estrogen impostors that block sex hormone production. The result could be falling sperm counts, as found in 1992 by Danish researchers who performed a meta-analysis of 61 studies worldwide, and concluded that mean sperm concentrations have been cut almost in half between 1940 and 1990. The world's attention was riveted to the finding, especially when University of Florida researcher Louis Guillette, who reported similar findings in alligators, told a congressional committee, "every man in this room is half the man his grandfather was." But the Danish findings are controversial; some scientists analyzed the same data and found increasing sperm counts, while others say sperm production can be affected by venereal disease, and the

difference in rates of venereal disease may account for the findings.

Another theory is that prenatal exposures to estrogens are responsible for rising numbers of testicular cancers. That link was explored by John McLachlan, director of the Center for Bioenvironmental Research at Tulane University, who found several decades ago that the synthetic estrogen diethylstilbestrol disrupted fetal testicular development, producing undescended testes and lower sperm counts. Since then, researchers have found dozens of chemicals, from pesticides to the plastic resin that lines food cans, that may disrupt the endocrine system via the estrogen receptor, and further investigation has found that estrogen mimics may act in different ways, producing various responses. The pollutant DDT has been found to produce testicular cancer in male rodents, while exposure to PCBs produced enlarged testes and increased sperm production in laboratory rats. Rex Hess, the University of Illinois researcher who reported growth of the enlarged testes at this year's meeting of the Society of Toxicology, says he thinks there is a critical window in male development where even a small extra amount of estrogen will produce delayed, harmful effects. "If you expose the organ to estrogen before it is ready, the organ may be impaired so that it can't function normally in adults. The toxic effect would be delayed."

In that context, some research findings make sense. For example, one study found that young black men had serum testosterone levels that are 15% higher than their white counterparts, accounting for their increased risk of developing the cancer. Similarly, other research determined that pregnant black women consistently had higher levels of estrogen than white pregnant women.

Gail Prins, a reproductive physiologist at the University of Illinois, has shown how excess estrogens can affect the prostate gland. Prins administered a single high dose of estrogen to rats on days one, three, and five after their birth, a critical time during development of the rat prostate gland (analogous to the second and third trimester in humans). She found a majority of the rats later developed prostate cancer. "This makes a compelling case, as much as you can make an analogy between rodent and human uterine exposure of estrogen," says Prins. She is now trying to uncover the actual mechanism—perhaps growth factors or increased DNA transcription—by which early estrogen exposure leads to prostate damage.



Ken Korach—Estrogen is a possible player in prostate and testicular cancers.

Steve McCaw, Image Associates

On the other hand, the dangers of no estrogen exposure have been revealed in an estrogen knock-out mouse produced in the NIEHS lab of Ken Korach, chief of the Receptor Biology Section. The consequences for both genders of the knock-out mouse was a tendency to infertility, Korach found. "It had a dramatic effect on the testes, reducing them to one-half their normal size in adult males. This means that estrogen has a real role in male reproduction," Korach has found that animals exposed to too much estrogen during a critical period of genital development have reduced sperm counts: "It's possible that the estrogen feedback system is disrupted, and sperm production is suppressed," he says. But Korach cannot yet say that estrogen balance is emerging as a primary actor in prostate or testicular cancer. "Right now, it should be considered a possible player."

Several highly publicized studies in the late 1980s reported that men who had vasectomies were more likely to develop prostate cancer because of high levels of testosterone circulating in the blood. But more recent data have discounted that argument, attributing the rates to better reporting as these men were more likely to see physicians about urologic complaints.

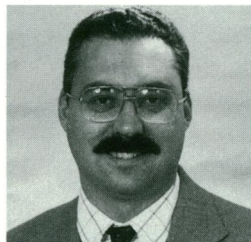
The hormonal surge brought on by frequent sexual activity is also a risk factor, physicians at the Harvard School of Public Health reported in the May 20 issue of the *British Medical Journal*. Frequent sex triggers excess testosterone and DHT production, which promotes cell division in normal prostate functioning. Harvard physician Christos Mantzoros says in the report that high DHT levels might spur cancerous cell proliferation. Based on the fact that men who cannot produce DHT never develop prostate cancer, the NCI is now sponsoring an 18,000-patient trial of the drug finasteride, which controls noncancerous prostate enlargement by controlling DHT levels.

Hormone-modulating chemicals, such as dioxin, a by-product of wood-pulp bleaching, seem to work in other sinister ways. Dioxin appears to affect both the prostate and the testes because it decreases, by up to 80%, "the amount of sperm available to ejaculate," says University of Wisconsin toxicologist Richard Peterson. "Sperm production is slightly lessened, but sperm storage is greatly hampered. And the most robust effects occur at the lowest levels. Dioxin is in a class of chemicals that merit more research because there is already a certain background level in utero and through lactate exposure."

According to Korach, "Dioxin also alters liver steroid metabolism, resulting in a possible hormonal imbalance."

Risky Business

Some researchers are questioning how a man's occupation might affect his reproductive health. Research this year from the Memorial Sloan-Kettering Cancer Center suggested extreme high (above 80°F) and low temperatures (less than 60°F) over a number of years during work may be a risk factor for testicular cancer, since the testis is a temperature-sensitive organ. The study, presented in the *Archives of Environmental Health*, found a significant risk factor for men exposed to high temperatures in their work environment for more than 10 years. And a study presented in 1994 from Kansas State University said that farmers in that



Michael Waalkes—Male cancers are multifactorial diseases.

state were at significantly higher risk for some cancers, including prostate cancer. The researcher, R. Scott Frey, told participants at the American Public Health Association meeting that data on almost 70,000 farmers indicate that there may be something in the farm environment, such as pesticides, that increases their cancer risk. But he added the results are preliminary, and more research is needed to assess the full scope of underlying causes of the cancer risks that Kansas farmers face.

Finally, several studies have looked at whether the trace mineral cadmium, found in welding shops, increases the risk of prostate cancer by reacting with zinc; the prostate has the highest concentration of zinc of any organ in the body. Michael Waalkes, a researcher at NCI's Frederick Cancer Research and Development Center, has found that both a rat's prostate and testes are sensitive to the chemical, which can cause cancer. But, Waalkes says he can't yet make the leap to saying that human glands are damaged. "It's difficult to say what portion of the rat prostate is analogous to the human prostate, so I don't think there is a good rat model there. And there is no good animal model for testicular cancer."

"All in all, I think that both of these male cancers are multifactorial diseases," says Waalkes. Like all researchers who seek to solve these complex biological riddles, he says the real question is which risk factor is the most important. Figuring this out will require continuing basic research into both male and female reproductive biology and toxicology to understand how environmental chemicals may exert their influence.

Renee Twombly

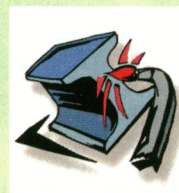
Factors



The gene that codes for an enzyme that detoxifies environmental carcinogens is deactivated in almost all human prostate cancers. A gene that prevents the spread of prostate cancer has been found to be absent in animals with metastatic prostate cancer.



Exposure to environmental estrogens, particularly *in utero*, from pesticides, plastic resins, and other sources may disrupt the endocrine system, causing prostate and testicular cancers.



Certain occupations may carry higher risks for male reproductive cancers: extreme high and low temperatures may play a role in testicular cancers, and exposure to cadmium and zinc in welding shops may increase risk for prostate cancer.



Where a man lives may have a lot to do with his risk for prostate cancer: ethnic groups with high-fat diets show higher rates of incidence, and men who live in northern climates and receive insufficient levels of vitamin D from UV radiation have higher rates.